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Application of ecological and evolutionary theory to microbiome community dynamics across systems

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15 Abstract

16 A fundamental aim of microbiome research is to understand the factors that influence the assembly and
17 stability of host-associated microbiomes, and their impact on host phenotype, ecology and evolution.
18 However, ecological and evolutionary theories applied to predict microbiome community dynamics are
19 largely based on macroorganisms and lack microbiome-centric hypotheses that account for unique features
20 of the microbiome. This special feature sets out to drive advancements in the application of eco-evolutionary
21 theory to microbiome community dynamics through the development of microbiome-specific theoretical
22 and conceptual frameworks across plant, human and non-human animal systems. The feature comprises 11
23 research and review articles that address; (i) the effects of the microbiome on host phenotype, ecology and
24 evolution; (ii) the application and development of ecological and evolutionary theories to investigate
25 microbiome assembly, diversity and stability across broad taxonomic scales; and (iii) general principles that
26 underlie microbiome diversity and dynamics. This cross-disciplinary synthesis of theoretical, conceptual,
27 methodological, and analytical approaches to characterising host microbiome ecology and evolution across
28 systems addresses key research gaps in the field of microbiome research and highlights future research
29 priorities.

31 Host-associated microbiomes play fundamental roles in host phenotype, ecology and evolution.
32 Understanding the factors that influence microbiome assembly, diversity and stability in plant and animal
33 hosts is therefore a major avenue of microbiome research. However, the application of ecological and
34 evolutionary theory to microbiome community dynamics is complicated by features of the microbiome,
35 including horizontal gene transfer, rapid evolution, and the production of public goods and antimicrobial
36 compounds (1).

37 Microbiome research, made possible by recent advances in technological and analytical tools to
38 characterise the diverse assemblages of host-associated microbiota, has transformed our understanding of
39 the role of host-associated microbiota in health and disease, and ultimately, their ecology and evolutionary
40 trajectory (2–5). Given the significant influence of the microbiome on host health and disease susceptibility,
41 these microbial communities offer promising targets for the diagnosis, prevention and treatment of disease
42 in agricultural, veterinary and medical practice. Engineering host microbiomes is a tantalising challenge, with
43 potential for disease suppression and treatment in plant and animal hosts. However, given the complexity
44 and dynamic nature of these systems, success in predicting, managing, and ultimately engineering the
45 microbiome will need to incorporate both ecological and evolutionary principles (2).

46 Further advances in this field require researchers to develop and compare different model systems
47 to deconstruct the microbiome, and to develop new theories and models to encompass the complexity and
48 dynamics of the microbiome (e.g. rapid evolution, public goods, horizontal gene transfer). Comparison across
49 diverse systems enables collective progress in such endeavours, and overcomes organism-specific challenges,
50 such as (i) challenges in isolating and cultivating microbiota (6), (ii) an ability to manipulate microbiomes and
51 test infectivity in model systems that are not possible in human microbiome studies due to ethical
52 considerations, and (iii) the relative focus of funding/analytical effort on human microbiomes, providing
53 highly informative high-resolution longitudinal and cohort studies. Consequently, comparisons across
54 different model biomes and scales are necessary in order to better understand the ecology of host-associated
55 microbiomes. To this end, we sought to organise a special issue that highlights: (i) the effects of the
56 microbiome on phenotype, ecology and evolution; (ii) the application and development of ecological and
57 evolutionary theories to investigate microbiome assembly, diversity and stability in plant and animal hosts
58 across broad taxonomic scales; (iii) the general principles that underlie microbiome diversity and dynamics,
59 using dynamical systems thinking; and (iv) presents a cross-disciplinary synthesis of theoretical, conceptual,
60 methodological, and analytical approaches to characterising host microbiome ecology and evolution.

61 This Special Feature in *Proceedings of the Royal Society B* contains 11 articles, including six research
62 articles and five review articles that address the ecology and evolution of plant, human and non-human
63 animal microbiomes, to provide a cross-disciplinary synthesis of theoretical, conceptual, methodological, and
64 analytical approaches to characterising host microbiomes and their influence on host health, ecology and
65 evolution.

66 2. Effects of the microbiome on phenotype, ecology and evolution

67 The main driver of microbiome research is the growing evidence that host associated microbiomes
68 can and do shape phenotypic, ecological and evolutionary adaptation in the host. Among the functions of
69 the microbiome is the effect these microbial communities can have on pathogen colonization and disease.
70 Ossowicki and colleagues (7) exemplify this idea in their exploration of disease suppression in wheat (*Triticum*
71 *aestivum*) by soil-associated microbiota. They find that suppression of the pathogen, *Fusarium culmorum*, is
72 only conferred by 14% of soils, but that this protection can not simply be ascribed to presence/absence of
73 particular microbiota or function. Ascribing functions, such as disease suppression, to particular microbiomes
74 requires the ability to manipulate the interaction and can be relatively easily done for soils. However,
75 manipulating host-microbiota interactions in animal hosts is arguably a more challenging endeavour.
76 Greyson-Gaito and coauthors (8) explore the power of microbiota transplants for testing the impact of gut
77 microbiota on host health and phenotype, cautioning about the importance of considering the ecological
78 realism of the transplant when interpreting the results.

79 Leftwich and co-workers (9) explore the evolutionary potential of mixed modes of microbiota
80 transmission in animal hosts, simulating the impact of vertical transmission, environmental acquisition and
81 mixed modes of transmission and their evolutionary significance to host gut-microbiome relationships. The
82 impact of transmission mode on microbiome composition and function has obvious relevance to host
83 evolution and phenotype, with implications for reproductive isolation and speciation. Links between the
84 microbiome and host phenotype influence how hosts might respond to environmental change and stress,
85 especially in terms of how quickly the host can alter its physiology. Stothart and collaborators (10) tested this
86 idea by comparing the gut microbiomes of eastern grey squirrels in urban versus forest environments. They
87 find that, although environment itself is important, variation in the microbiome is more strongly explained
88 by measures of the hypothalamic–pituitary–adrenal hormonal system, which is indicative of recent stress in
89 the host.

90 Given the short generation time of microbial species relative to their hosts, there is clear reason to
91 expect evolutionary processes to be occurring within the microbiome over the course of a single host lifetime.
92 Scanlan explores this idea by focusing on mouse and human studies, arguing that these processes are not
93 only common but also critical to understanding and predicting host-microbiome interactions. Over longer
94 time-scales, exploring phylogenetic patterns of associations between hosts and their microbiomes has
95 proven an exciting way to infer their evolutionary relationships. Recent interest in ‘phylosymbiosis’, as
96 elegantly introduced by Lim and Bordenstein (11), has led to numerous comparisons of host-associated
97 microbiomes across host phylogenies (12). When detected, these patterns have been used to suggest both a
98 level of specificity in host-microbiome interactions and the potential role for microbiomes in shaping
99 speciation and vice versa. In this issue Trevelline and colleagues explore the potential for phylosymbiosis
100 across 15 species of cranes, all of which had been kept in the same environment and under the same diet
101 (13). They observed a pattern of phylosymbiosis, but only after incorporating absolute microbial densities
102 and removing male birds, suggesting interesting differences between birds and mammals (where patterns of
103 phylosymbiosis seem more robust).

104 3. Developing theoretical and conceptual frameworks for microbiome community dynamics

105 Ecological and evolutionary theories developed for macroecology are increasingly applied to explain
106 phenomena connected with host-associated microbiomes, but are ultimately constrained by the unique
107 features of the microbiome, the complexity of host-microbiota-environment interactions across space and
108 time, and a lack of microbiome-specific hypotheses and predictions. In recent decades, methodological and
109 analytical advances have led to an explosion in the generation of empirical data, but the development of
110 microbiome-focussed hypotheses, predictions and conceptual frameworks lags behind the generation of
111 these data (1,14). However, genotypic and phenotypic properties of microorganisms are tractable to
112 laboratory manipulation, and consequently, combinations of computational modelling and empirical studies
113 offer opportunities to test new hypotheses on the eco-evolutionary properties of the microbiome. Several of
114 the articles within this special feature develop and apply theoretical and conceptual frameworks that test
115 hypotheses regarding the eco-evolutionary drivers of host-microbiome interactions.

116 Angell and Rudi (15) describe a combinatorial game theory model that assessed the impact of
117 nutrient utilisation strategies of microbiota on composition of the infant gut microbiome. Their
118 computational model predicted initial mother-child transmission of specialists, followed by a shift to
119 generalist microbiota after 3 months of age in the immature expanding gut microbiome. The model
120 predicted that generalists are replaced by specialists after 12 months, during maturation of the human gut

121 microbiota. While the model simulations represent a simplified model of the system *in vivo*, it generates
122 important predictions of microbiome assembly and dynamics in the infant gut microbiome that can
123 subsequently be tested empirically to explain known patterns of alpha and beta diversity with age.

124 Biotic interactions are fundamental to microbiome stability, and Herren (16) further develops the
125 idea of cross-feeding and competition between microbiota by generating metabolite-explicit models to
126 assess the impact of microbial invasion on cross-feeding and competition. The model predicted that
127 microbiomes with stronger cross-feeding and competition exhibited lower invasion risk, but when invasion
128 was successful, diversity and productivity decreased and cross-feeding was disrupted. Scanlan (17) reviews
129 the role of rapid microbial evolution in the human gut, addressing key knowledge gaps surrounding the mode,
130 tempo and functional impacts of drift and selection, and their impact on microbial evolution in the gut
131 microbiome. This analysis is framed in the context of 'ecological opportunity', where environmental change
132 can alter niche availability, to ultimately affect persistence or displacement of members of the gut microbiota.
133 Leftwich and colleagues (9) address a lack of theoretical models to explore the transmission mode of
134 symbiotic microbiota in animal hosts using deterministic discrete generation mathematical models to
135 simulate population level associations between host animals and symbionts. In particular, the model
136 assessed vertical transmission, environmental acquisition, and mixed modes of transmission, in establishing
137 a conceptual framework which suggests that mixed modes of microbial transmission lead to the highest
138 frequencies of host microbe associations and ultimately transmission mode is important in establishing host
139 microbiome stability. These theoretical models lay the foundation for future empirical studies to test and
140 verify these theories.

141 Disease suppressiveness in soils confers resistance against root pathogens of plants and is typically
142 mediated by poorly characterised chemical interactions between bacterial microbiota. Consequently,
143 invasion success and ecological opportunity are important determinants of health and disease in plant
144 pathosystems. Ossowicki and co-workers (7) describe an extensive study of field soils for suppression of the
145 fungal pathogen *Fusarium culmorum*, using wheat as a model system. Gamma irradiation of soils and a lack
146 of correlation of physicochemical parameters with suppression confirmed that disease suppressive
147 phenotypes have a microbiological basis, but there was a lack of correlation of taxonomic diversity across
148 suppressive soils. As microbiota diversity and composition could not explain disease suppressive phenotypes,
149 the authors propose that several independent mechanisms may impart disease suppressive phenotypes on
150 different soils, including microbial volatile production in some and co-occurrence of specific taxa (e.g.
151 *Acidobacteria*) in others.

152 Microbiomes play fundamental roles in health and disease. In the context of plant health, Doonan
153 and colleagues (18) investigated the role of host-microbiota-insect interactions in the Acute Oak Decline
154 (AOD) pathosystem. AOD is a complex decline disease where the cumulative effects of several abiotic
155 (environmental) and biotic (bacterial pathogens and bark boring beetles) factors result in stem tissue necrosis
156 and disruption of nutrient and water flow, often leading to rapid decline and death of the tree. Virulence has
157 been described as an emergent property (19). Emergent properties cannot be explained by their individual
158 components, and the outcome of these interactions is greater than the sum of its individual parts and not
159 irreducible to their individual components (19). Using emergent virulence as a conceptual framework to
160 assess the interactions between the host, microbiota and insects in AOD, Doonan and colleagues (18)
161 combined reductionist (RNAseq analysis of single and dual cultures of bacterial species) and emergentist
162 approaches (log infection tests inoculated with insect larvae and bacterial cultures) to demonstrate the
163 emergent properties of microbe-microbe and host-microbiota-insect interactions. These experiments
164 revealed cooperation between key bacteria associated with tissue necrosis in affected trees, and in the
165 presence of beetle larvae, gene expression of bacterial virulence genes and symptom severity (tissue
166 necrosis) were amplified, demonstrating the emergent properties of microbiota-host-insect interactions in
167 AOD symptomology.

168 Lim and Bordenstein (11) review the concept of phylosymbiosis; '*microbial community relationships*
169 *that recapitulate the phylogeny of their host*' (20). Such relationships between microbiota composition and
170 related host species are detectable in many plant and animal hosts, and are regulated by mechanisms that
171 are ripe for future investigations, and reliant upon appropriate conceptual, empirical and analytical
172 approaches that are reviewed here (11). Trevelline and co-workers (13) present an empirical study of the gut
173 microbiota of 15 captive crane species, detecting weak signatures of phylosymbiosis. Interestingly,
174 incorporation of absolute microbial cell density data obtained by flow cytometry with 16S rRNA gene profiles
175 of microbiota composition improved the strength of the signal of phylosymbiosis. The concept of
176 phylosymbiosis, combined with the methodological roadmaps presented in this special feature, provides a
177 hypothesis-driven framework for future studies of microbiota composition across host systems, and to
178 understand eco-evolutionary processes that shape host-microbiota interactions. Knowledge of the
179 composition of the microbiota in relation to host phylogeny and the eco-evolutionary processes that shape
180 these interactions are important considerations in microbiome transplant experiments, and in the
181 production of precision microbiome treatments that are at the forefront of the field of microbiome research.

182 To guide future developments in microbiota transplant research, Greyson-Gaito and colleagues (8)
183 propose the concept of ecological reality (or 'EcoReality'). They review studies that report microbiota
184 transplants in non-human animals and identify experimental factors that impact the ecological reality of the
185 experiment. The authors use this to generate a conceptual framework to guide improvements in the
186 EcoReality of future empirical research studies where microbiota are transplanted. Such approaches are
187 critical to enhance our prospects of leveraging host microbiomes, for example, in the sustainable
188 development of teleost aquaculture where microbiome manipulation has the potential to influence host diet,
189 immunity, welfare and selection to support this burgeoning industry of fisheries and aquaculture (21).

190 Collectively, these studies advance micro-ecological theory through consideration of the role of game
191 theory, ecological opportunity, microbial invasion, rapid evolution, cross-feeding, diseases suppression,
192 emergent virulence and phyllosymbiosis in microbiome assembly, stability and dynamics. Moving forward,
193 these theoretical and conceptual frameworks will facilitate the generation of specific hypotheses that allow
194 us to predict and test microbiome composition and function, with potential to inform the manipulation and
195 transplantation of microbiota for precision treatment, guided by knowledge of the factors that drive
196 microbiome assembly and a quest for ecological reality in empirical studies.

197 4. Methodological and analytical approaches for characterising host microbiomes

198 The development and testing of ecological and evolutionary theories that incorporate the
199 microbiome is important to enhance knowledge and understanding of host-microbiota interactions and their
200 effects on eco-evolutionary processes (1), and to move beyond descriptive accounts of microbiome
201 composition (22). Such advances require the development of theoretical and conceptual frameworks such as
202 those discussed in section 3 to drive hypothesis generation and predictions that can be tested through the
203 careful design of empirical studies. The field of microbiome research therefore transcends disciplines, as
204 exemplified by the diversity of methodological and analytical approaches described in the contributions to
205 the special feature, including mathematical modelling (9,15,16,18), DNA and RNA sequencing (7,10,13,18),
206 flow cytometry (13), infection tests in model and non-model pathosystems (7,18), physicochemical and
207 volatile analysis (7), and measures of hormone activity to assess host physiological responses to its
208 environment (10).

209 A major theme pervading this special feature is the link between mathematical model simulations
210 and empirical studies (9,15–17). Angell and Rudi (15) compared probabilistic model simulations with
211 empirical observations to test whether a game theory model of generalist or specialist nutrient utilisation

212 strategies could explain assembly and dynamics of the infant gut microbiome. In this study, development
213 of a generalist-specialist model that extends the host selection model to incorporate combinatorial game
214 theory with nutrient utilisation best described the observed patterns of microbial diversity and function in
215 the empirical data. Leftwich and co-workers (9) developed deterministic discrete generation mathematical
216 models to assess the potential role of mixed modes of microbiota transmission on evolutionary potential in
217 animal systems. Such modelling approaches are valuable, as they facilitate the development of theoretical
218 frameworks on which future empirical studies can be designed to test and validate model predictions.

219 Lim and Bordenstein (11) reviewed recent data on signals of phyllosymbiosis in microbiomes, and
220 present an analytical framework for the quantitative analysis of phyllosymbiosis across host taxa. They
221 suggest that adoption and expansion of this workflow could lead to improved identification of patterns of
222 phyllosymbiosis and enhance opportunities to understand the role of ecological and evolutionary processes in
223 host microbiome associations. Microbiome transplant studies represent an important and increasingly
224 applied approach to characterise host-microbiota interactions. While stating that although there is a clear
225 need for highly controlled microbiome transplant experiments, Greyson-Gaito and colleagues (8) reviewed
226 the breadth of ecological reality in microbiome transplant studies and identified nine experimental
227 conditions that affect EcoReality. Their analysis suggests that the 'EcoReality' of microbiota transplant studies
228 has increased over time, and they present a roadmap for enhancing EcoReality in future transplantation
229 experiments. Following this theme, Doonan and colleagues (18) describe the emergent properties of host-
230 microbiota-insect interactions that drive Acute Oak Decline (AOD), a complex decline disease of oak trees.
231 They combined *in vitro* transcriptome experiments comprising single and poly-species bacterial cultures
232 growing on oak tissue, with more complex infection tests combining bacterial inoculations with the addition
233 of beetle larvae in a novel oak log infection model, to demonstrate the cumulative impact of these
234 interactions on the pathology of AOD. Ossowicki and co-workers (7) used soil transplantation experiments to
235 demonstrate the microbiological basis of disease suppression in wheat (*Triticum aestivum*) to the soil
236 pathogen *Fusarium culmorum*, providing fascinating insights into the mechanistic diversity of disease
237 suppression in soils.

238 5. Factors that shape microbiome assembly, diversity and stability in hosts across broad taxonomic scales

239 In testing hypotheses derived from theoretical and conceptual frameworks discussed above, this
240 special feature explores several different factors that shape the assembly and stability of host associated
241 microbiomes, integrating knowledge from across systems that include plants, humans, insects, birds,
242 rodents, and teleost fish. The human gut microbiome has arguably received greater research focus than other

243 host systems, but comparing microbiome assembly and dynamics across broad systems provides fertile
244 ground for hypothesis design and empirical testing. Combinations of reductionist approaches and more
245 complex experiments *in vivo* for model systems where they are more amenable, for example where ethical
246 considerations are less restrictive compared to human microbiome studies (e.g. infection tests and
247 microbiota transplants in plants), provide excellent opportunities to explore such hypotheses (18).

248 Angell and Rudi (15) investigated factors that shape the assembly, dynamics and diversity of the
249 infant gut microbiota within the first 12 months of age. Combining game theory simulations that
250 encompassed generalists and specialists, their models matched empirical data and predicted increased alpha
251 and reduced beta diversity with age, highlighting initial competitive advantage of generalists with a transition
252 to more specialised bacteria during maturation. Metabolic cross-feeding is ubiquitous across microbial
253 communities, with implications for community assembly and stability in terms of biotic interactions and
254 invasion. Herren (16) developed a metabolite-explicit model which predicted that stronger cross-feeding
255 between microbiota reduced invasion risk, but when invasion was successful (under intermediate levels of
256 cross-feeding), cross-feeding, productivity and diversity was reduced, which increased the risk of secondary
257 invasion. Microbiota may be vertically transmitted with their hosts, acquired environmentally, or through
258 mixed modes of transmission (vertical and horizontal), and can lead to stable co-associations. Leftwich and
259 colleagues (9) developed deterministic mathematical models to simulate conditions which promoted stable
260 co-associations between hosts and their microbiota. They observed that transmission mode was an
261 important criterion for host-microbiota stability, with mixed modes of transmission resulting in greatest host-
262 microbiota associations.

263 Rapid evolution of microorganisms across time and space, and their functional consequences, is an
264 important yet poorly studied phenomena in the context of host-associated microbiomes. Scanlan (17)
265 discusses the impact of rapid evolution and ecological opportunity on bacterial adaptation, colonisation and
266 persistence in the gut microbiome, and suggests combined experimental evolution and genomic approaches
267 to identify drivers of evolution in the microbiome. Niche availability and niche discordance are key factors
268 that govern the capacity for a lineage with a certain phenotype to persist in an environment. Two relevant
269 empirical studies in this special feature also address the functional interactions between plant hosts,
270 microbiota and the environment in the context of plant disease (7,18).

271 Host phylogeny and physiology may also shape the composition of host microbiomes. Phyllosymbiosis
272 describes higher microbiome diversity between species than within host species and is observed by
273 comparing host phylogenies and microbiome dendrograms and observing relationships between microbiome

274 beta diversity and host genetic relationships (discussed by Lim and Bordenstein (11)). Trevelline and
275 colleagues detected weak phylosymbiotic signals in 15 species of cranes when male individuals were
276 removed from the analysis and microbial cell density counts were included, leading to a suggestion that
277 transmission route and host filtering impact the strength of phylosymbiotic signals. Changes in a host's
278 environment may also influence its microbiome; however a key question in microbiome research is whether
279 microbiome restructuring is driven predominantly by the external environment changes, or the host's
280 physiological response to this change. Stothart and co-workers (10) test this hypothesis in by analysing the
281 impact of urbanisation on grey squirrel populations, suggesting that impacts of environmental change on the
282 microbiome occur indirectly through altered effects on host physiology. Perry and colleagues (21) provide an
283 insightful discussion of the deterministic forces that drive microbiome dynamics and function in sustainable
284 telost aquaculture and highlight research gaps and future opportunities for microbiome manipulation.

285 6. Conclusions and future research priorities.

286 This special feature addresses key research gaps in microbiome research by developing theoretical
287 and conceptual frameworks to describe factors that influence microbiome assembly and stability, including
288 a generalist/specialist game theory model of infant gut microbiome maturation (15), a metabolite-explicit
289 model of microbial cross-feeding and invasion (16), and theoretical models on the role of mixed modes of
290 transmission on stable host-microbiota associations (9). Additional advances include conceptual and
291 methodological frameworks for detection of host-phylogeny and microbiome relationships (11,13), rapid
292 microbial evolution and ecological opportunity in gut microbiomes (17), and approaches to enhance
293 ecological reality of microbiome transplant studies (8). The deterministic assembly of teleost fish
294 microbiomes, and possibilities for microbiome manipulation for sustainable aquaculture is also discussed
295 (21). Empirical studies applied the theory of emergent virulence to demonstrate the emergent properties of
296 complex host-microbiota-interactions in the context of a plant disease (18), the impact of host physiology on
297 the microbiome (10), and the role of soil microbiota in disease suppressive phenotypes of plants and soil
298 transplantation to confer pathogen resistance (7).

299 Moving forward, it is important the the field of microbiome research continues to develop ecological
300 and evolutionary theories that incorporate the microbiome and its unique features, and that they are
301 subsequently tested empirically using complementary, transdisciplinary approaches. A key theme emanating
302 from this feature is the power of combining complementary approaches from different disciplines to address
303 such questions. In addition to providing new theoretical and conceptual models to assess the ecology and
304 evolution of host-associated microbiomes, the articles presented in this special feature also highlight ongoing

305 research gaps and future research priorities for the field, including; (i) the validity of highly controlled
306 microbiome transplant experiments, but guidelines for broadening EcoReality in future experiments (8), as
307 appropriate, (ii) greater consideration of host physiology and its impacts on microbiome assembly and
308 dynamics (10), (iii) the need for applied experimental evolution studies to characterise rapid evolution within
309 microbiomes (17), and (iv) integrated theoretical, conceptual and empirical approaches are required to
310 address complex host-microbiome-environment interactions. This may include combinations of
311 experimental evolution and genomics approaches to study rapid evolution and functional consequences (17),
312 host physiology (10), applying conceptual frameworks for statistical analysis of quantitative signals of
313 phyllosymbiosis across taxa (11,13), microbiota transplants (7,8), or the combination of reductionist and
314 emergentist approaches to disentangle complex host-microbiota-insect interactions associated with disease
315 (18).

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